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(57) Abstract			
<p>A drug delivery device includes a liquid reservoir (24) for a liquid drug to be delivered, and a drug delivery body which includes a plurality of tubular elements (26) or hollow needles extending through the body, each having an inlet end communicating with the liquid reservoir, and an outlet end projecting from the body and engageable with the subject's skin to conduct the liquid drug directly to the subject's skin.</p>			

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DRUG DELIVERY DEVICES

The present invention relates to transdermal or interdermal drug delivery devices for delivering a liquid drug to a subject via the subject's skin. The invention is particularly useful with respect to the drug delivery device described in our Patent No.5,156,591, and is therefore described below with respect to that device, but it will be appreciated that the invention could advantageously be used in other types of drug delivery devices.

Our Patent No.5,156,591 describes a transdermal drug delivery device which delivers a drug to the subject by means of an electrically-induced mass transfer phenomenon called iontophoresis. This process for drug delivery has recently become of great interest, and many such transdermal delivery devices have been described in the patent literature, including US Patents 4,164,226, 4,640,689, 4,708,716, 4,752,285, 4,693,711, 5,057,072, US Statutory Invention Registration H516, and European Patent Application Publication 0299631. Other methods of electrically-aided or electrically-controlled transdermal drug delivery devices are described in US Patent 4,886,513, as well as in our prior US Patents 5,062,834 and 5,090,963.

According to the present invention, there is provided a drug delivery device for delivering a liquid drug to a subject via the subject's skin, comprising: a housing; a liquid reservoir in the housing for a liquid drug to be delivered; and a drug delivery body carried by the housing and having one side communicating with one side of the liquid reservoir, and the opposite side exposed to engage the skin of the subject to receive the drug; characterized in that the drug delivery body includes a plurality of stiff tubular elements extending through the body, each having an inlet end communicating with the liquid reservoir, and an outlet end at said opposite side of the drug delivery body to conduct the liquid drug directly to said opposite side.

The plurality of stiff tubular elements may be in the form of hollow needles having inner diameters of less than 1 mm and projecting at least 0.1 mm from the face of the drug delivery body. Preferably, the drug delivery body includes at least fifty of such stiff tubular elements or hollow needles. Their tips may be cut at a bias to pierce the outer layer of dead cells on the skin and thereby to enhance the penetration of the drug.

In the use of the device, the plurality of tubular elements are pressed firmly against the subject's skin, and thereby provide a better delivery of the drug to the subject's skin, as compared to the use of microporous or matrix-type drug delivery bodies as in the prior art. The device also permits better control of the drug delivery rate. When the delivery is effected by iontophoresis, the better delivery of the drug enables lower electrical currents to be used, thereby decreasing the danger of burning or irritating the subject's skin.

Fig. 1 is a top plan view illustrating one form of transdermal drug delivery device constructed in accordance with the present invention;

Fig. 2 is a bottom plan view of the device of Fig. 1;

Fig. 3 is an enlarged sectional view along line III-III of Fig. 2;

Figs. 4, 5 and 6 are views similar to that of Fig. 3 but illustrating three further forms of drug delivery devices constructed in accordance with the present invention;

and Figs. 7a-7e illustrate various tip constructions of the stiff tubular elements extending through the drug delivery body.

The transdermal drug delivery device illustrated in Figs. 1-3 of the drawings, and generally designated 2, is applied by a band 3 to the arm or leg of the subject, with one side of the device (that side illustrated in Fig. 2) firmly pressed against the subject's skin. The device 2 is

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a self-contained unit which includes a reservoir for the liquid drug to be delivered, as well as electrodes for delivering the drug by means of the iontophoresis electrically-induced mass transfer phenomenon. Device 2 further includes an electrolytic cell which, together with the iontophoresis electrodes, controls the rate of feed of the drug to the subject, and an electrical battery for powering both the iontophoresis electrodes and the electrolytic cell.

10 The internal structure of the transdermal drug delivery device 2 is more particularly illustrated in Fig. 3. It includes a housing 4 of plastic material and of circular configuration. Housing 4 is made of an inner section 4a, an outer section 4b, and an intermediate section 15 4c threadedly joining sections 4a and 4b together. The inner section 4a is formed with a large circular opening 6, and the outer section 4b is formed with a smaller circular opening 8.

An inner membrane 10 is clamped between housing 20 sections 4a and 4c, and an outer membrane 12 is clamped between housing sections 4b and 4c. Both membranes 10 and 12 are of elastomeric material and include annular flexible sections 10a, 12a, to make them displaceable in response to pressure. Membrane 10 is aligned with the center opening 6 25 in housing section 4a and is clamped between that housing section and the intermediate section 4c via a ring 14. Membrane 12 is clamped between the intermediate housing section 4c and the outer housing section 4b via a disc 16 having a central opening 18 in alignment with opening 8 in 30 the outer housing section 4b. A third membrane 20 is clamped between disc 16 and the outer housing section 4b to close opening 8.

Membrane 10 is displaceable outwardly of housing 4 by its annular flexible section 10a, but is restrained 35 against inward displacement by a rigid annular disc 22 integrally formed with the intermediate housing section 4c. Membrane 12, however, is displaceable in both directions by

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its annular flexible section 12a. Membrane 20 is similarly displaceable in both directions with respect to openings 8 and 18 in housing section 4b and disc 16, respectively.

The two membranes 10, 12 define, between them, a chamber 24 serving as a liquid reservoir for the liquid drug to be delivered by the device 2. Membrane 10 serves as a drug delivery body through which the drug is delivered. For this purpose, membrane 10 includes a plurality of tubular elements 26 extending through it, with each tubular element having an inlet end 26a communicating with the liquid reservoir 24, and an outlet end 26b engageable with the subject's skin.

A second chamber 28 is defined between membrane 12 and disc 16 and its membrane 20. Chamber 28 serves as a pressure-control chamber for controlling the pressure applied to the drug chamber 24 for controlling the rate of feed of the liquid drug via tubular elements 26 through the drug delivery membrane 10. For this purpose, chamber 28 includes an electrolytic cell, generally designated 30, comprising a pair of electrodes 30a, 30b and an electrolyte 30c which generates a gas in accordance with the current passing through it. Such electrolytic cells are well known and are capable of generating a gas (e.g., oxygen and/or hydrogen) when an electrical current is applied.

Electrolytic cell 30 is located in one side of a cavity formed in membrane 12. The other side of the cavity serves as a compartment for a button-type battery 32 powering the electrolytic cell 30. Electrode 30a of the electrolytic cell is connected to one side of the battery via spring clips 34a and 34b electrically connected together by lead 34c, all carried by disc 16. Electrode 30b of the electrolytic cell is extended so as to engage the other side of the battery 32.

Battery 32 also supplies electrical current to a pair of iontophoresis electrodes 36, 38, to induce the transfer of the drug within compartment 24 via the tubular elements 26 in membrane 10 to the subject's skin. Electrode

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36 is of annular shape and encloses membrane 10 so as to come into contact with the subject's skin when the device 2 is applied to the subject. Electrode 38 is a conductive layer applied to membrane 12 facing the drug compartment 24 so as to come into direct contact with the drug therein.

The drug is introduced into the drug compartment 24 via an injection port 40 received in an opening on one side of the intermediate housing section 4c. A nipple 42 is threadably applied in alignment with an opening in the 10 opposite side of the intermediate housing section 4c and is closed by a hydrophobic filter 44. The liquid drug is introduced into drug compartment 24 via an injection syringe piercing plug 40. Nipple 42 serves as a vent for purging the air from compartment 24 until the vent is closed by 15 contact of the liquid drug with the hydrophobic filter 44 when the compartment is filled with the drug.

Membrane 10 is made of a reslient, deformable material. The tubular elements 26 passing through membrane 10 are preferably made of a stiff, i.e., rigid or semi-rigid, plastic material having an inner diameter of less than 1.0 mm, and projecting at least 0.1 mm from the outer face of membrane 10. As examples, these tubular elements 26 may be made of Teflon (Reg. TM), or of a polycarbonate resin, have an outer diameter of 1.0 mm, an inner diameter of 0.5 mm, and projecting about 0.3 mm from the surface of the drug delivery membrane 10 in contact with the subject's skin. Preferably, they are in the form of hollow metal needles, such as of steel or aluminum coated on their outer suraces with a coating of insulation, e.g., by oxidation, chemical deposition, etc.

A drug delivery device would usually include at least 50 of such tubular elements, with the outlet ends 26b of each such element firmly engaging the subject's skin so as to effectively seal their inner channels to the subject's skin. These tubular elements thus deliver the drug from compartment 24 directly to a multitude of spaced discrete areas on the subject's skin, and at a rate determined by the

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pressure applied to the drug chamber 24 by the displacement of membrane 12.

As one example, membranes 10, 12 and 20 may be of a silicone rubber. Electrically-conductive layer 38 applied 5 to membrane 12, and/or electrode 36 applied to the subject's skin, may also be of a silicone rubber, but with an electrically-conductive filler such as silver, carbon or aluminum particles.

The device illustrated in Figs. 1-3 may be applied 10 to the arm or leg of the subject to receive the drug by the use of the bands 3 such that the inner face of the device, illustrated in Fig. 2, firmly engages the subject's skin. When the device is so applied, the outer ends 26b of the stiff tubular elements 26 passing through the drug-delivery 15 membrane 10 project slightly from the membrane and firmly engage the subject's skin.

Battery 32 supplies electrical current via an electrical switch or other control circuitry (not shown) to both the electrolytic cell electrodes 30a, 30b and to the 20 iontophoresis electrodes 36, 38.

The electrolytic cell 30 generates a gas in accordance with the magnitude of the electrical current applied to its electrolyte 30c. This gas increases the pressure within chamber 28 to displace membrane 12 towards 25 membrane 10, thereby increasing the pressure within the drug chamber 24. Membrane 20, having one side exposed to the pressure within chamber 28 and the other side exposed to the atmosphere, tends to regulate the pressure within chamber 28.

30 The displacement of membrane 12 towards the drug delivery membrane 10 forces the liquid drug from compartment 24 through the tubular elements 26 in accordance with the pressure in chamber 24. The pressure in chamber 24 also tends to displace membrane 10 outwardly, thereby more firmly 35 pressing the outlet ends 26b of the tubular elements 26 into contact with the subject's skin. It will thus be seen that the rate of feeding of the drug from chamber 24 via tubular

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elements 26 to the subject's skin will be controlled by the rate of generation of gas by the electrolytic cell 30.

The transfer of the drug from compartment 24 to the subject's skin is electrically-induced by the voltage applied between the two iontophoresis electrodes 36 and 38. Electrode 36 directly contacts the subject's skin, and electrode 38 directly contacts the drug within compartment 24 delivered to the subject's skin via the tubular elements 26.

It will thus be seen that the delivery of the drug from compartment 24 to the subject's skin is effected in a manner which is both efficient and controllable by controlling the electrical current supplied to the electrolytic cell 30 and also the voltage applied between the two iontophoresis electrodes 36, 38.

Fig. 4 illustrates another device which is generally similar to that of Fig. 3 but includes a number of changes. To facilitate understanding, the elements in the device of Fig. 4 which are generally similar to those in Fig. 3 are correspondingly numbered.

One important difference in the device of Fig. 4 over that of Fig. 3 is that the housing 4 is a two-section housing (rather than a three-section housing), including the two sections 4 and 4b threadedly secured together. The injection port 40 for introducing the drug into the drug reservoir in compartment 24 is located within an opening in housing section 4a.

Another difference in the construction of the device of Fig. 4 over that of Fig. 3 is that the drug delivery body for delivering the drug from the drug compartment 24 is constituted, not by a displaceable membrane 10, but rather by the rigid wall 50 of housing section 4a, which rigid wall carries the stiff tubular elements 26 communicating with the drug compartment 24. Thus, the device of Fig. 4 does not include a membrane corresponding to membrane 10 in Fig. 3.